REMARKS

A. Objection to the Declaration

The Examiner objected to the declaration because it incorrectly claims to priority to Provisional Application No. 60/097,864, rather than Provisional Application No. 60/097,846. As noted by the Examiner in the 8/26/02 office action, Applicant has indicated and will submit a substitute declaration correcting this typographical error.

B. Rejection of Claims 17-19 and 21-23 Under 35 U.S.C. § 112, ¶ 1 for Lack of Written Description

The Examiner rejected claims 17-19 and 21-23, maintaining the rejection as set forth in Papers No. 13 and 11, mailed 1/09/02 and 7/05/01 respectively. The Examiner states that there is a lack of sufficient written description in the specification to reasonably convey to one of ordinary skill in the relevant art that the inventor had possession of the claimed invention as of the earliest priority date of the pending application, August 25, 1998. Reconsideration is requested in light of the declaration of Dr. Martin Acquadro attached hereto, and in light of the following comments.

With respect to these claims, the Examiner failed to find support in the specification for "a method for treating neurogenic inflammation" and "at least one neurogenic inflammatory mediator". Applicant believes that support for these aspects of the invention are found amply throughout the specification.

Applicant submits herewith the declaration of Dr. Martin Acquadro, an expert in the fields of inflammation, pain, and Botulinum Toxin

applications. Attached to his declaration is a copy of his Curriculum Vitae showing that he is an expert in these fields.

It is settled law that expert declarations should be given substantial weight by the Examiner in overcoming 35 U.S.C. § 112 rejections. *In re Alton*, 76 F.3d 1168, 1175 (Fed. Cir. 1996) (Holding that the patent examiner erred in viewing the expert declaration as opinion evidence addressing a question of law rather than a question of fact). The Federal Circuit has made it clear that the question of whether a specification provides an adequate written description of the subject matter of the claims is an issue of fact. *Id.* at 1174. In accordance with this controlling precedent, the Applicant respectfully asserts that the Examiner must treat Dr. Acquadro's declaration as factual evidence of the adequacy of the specification of the instant application as a written description of the invention as claimed. *Id.*

Dr. Acquadro has reviewed the pending application and the relevant art, and has determined that one of ordinary skill in the art, when reading the specification as a whole as of the earliest priority date of the pending application, August 25, 1998, would understand that the disclosure clearly describes the treatment of neurogenic inflammation and the anatagonism of at least one neurogenic mediator, and demonstrates that as of the earliest priority date of the pending application, August 25, 1998, the inventor was in possession of the invention as so claimed. (Acquadro Decl., ¶4 & 6).

For example, he points out in paragraph 6 of his declaration that the explicit disclosure of mast cell and nerve cell release of "performed mediators" and the blockage of such release by chemodenervating pharmaceuticals, such as botulinum toxin, would be clearly understood by one of ordinary skill in the art as referring to neurogenic inflammation and neurogenic mediators, and as indicating that the inventor had the invention as claimed in claims 17-19, and 21-23 in his possession as of the earliest priority date of the pending application, August 25, 1998.

Dr. Acquadro further directs the Examiner's attention to language in the specification demonstrating one of ordinary skill in the art would understand that the specification describes a method of treating neurogenic inflammatory as of the earliest priority date of the pending application, August 25, 1998. This language is as follows:

- "[A]nti-inflammatory action is explained by resultant blockage of mast cell and nerve cell release of histamine and other preformed mediators which result in vascular dialation, increased permeability, altered sensory experience, edema and erythema." (Third paragraph of "Summary of Invention"); (Acquadro Decl. ¶7).
- "[C]hemodenervative pharmaceuticals such as botulinum toxin...are effective anti-inflammatory agents." (Second paragraph of "Summary of Invention"); (Acquadro Decl. ¶8).
- "The subject anti-inflammatory agent's unique property relates to the suppression of the component for the inflammatory response which occurs rapidly, and which is

mediated by neural reflex mechanisms." (Sixth paragraph of "Summary of Invention"); (Acquadro Decl. ¶8).

- "[I]nflammation in torticollis in peripheral tissues may be neurogenically mediated." (Third paragraph of "Spasmodic Torticollis"); (Acquadro Decl. ¶9).

Indeed, one of ordinary skill in the art, when reading the specification as a whole, would understand that the disclosure describes the treatment of neurogenic inflammation and the antagonism of at least one neurogenic mediator. All of the extensive discussion throughout the specification of mast cell and nerve cell release of "preformed mediators" and the blockage of such release by chemodenervating pharmaceuticals, such as botulinum toxin, would be clearly understood by one of ordinary skill in the art as referring to neurogenic inflammation and neurogenic mediators, and as indicating that the inventor had the invention as claimed in claims 17-19, and 21-23 in his possession at the time of filing. (Acquadro Decl., ¶6).

The Examiner also states that he fails to understand the logic of the argument that what is disclosed in the '768 patent, which issued at a later date, is encompassed in the instant application. The Applicant respectfully request that the Examiner consider this reference as evidence of how one of ordinary skill in the art would have understood the instant application's specification as of the earliest priority date of the pending application, August 25, 1998.

Dr. Acquadro submits in paragraph 10 of his declaration that U.S. Patent No. 6,063,768 to First, entitled "Application of Botulinum Toxin to the Management of Neurogenic Inflammatory Disorders" ("'768 patent") demonstrates a level of understanding that one of ordinary skill in the art would possess as of the earliest priority date of the pending application, August 25, 1998. One of ordinary skill in the art would have understood, as of the earliest priority date of the pending application, that the disclosures in the specification enumerated above refer specifically to neurogenic inflammation. As Dr. Acquadro stated in paragraph 10, while the Examiner is correct in stating that the '768 patent was not issued until after the instant application's filing date, it was filed on September 4, 1997 and is a continuation-in-part of a September 6, 1996 provisional application. The '768 patent shows similar language pertaining to the treatment of neurogenic inflammation during a similar time period. Thus, the '768 patent provides the Examiner with evidence of how one of ordinary skill in the art would have understood the specification as of the earliest priority date of the pending application, August 25, 1998.

One of ordinary skill in the art would have understood as of the earliest priority date of the pending application that the disclosures in the specification enumerated above refer specifically to neurogenic inflammation. The '768 patent explains in some detail, with numerous references to the scientific literature how the term "neurogenic inflammation" would be understood by one of ordinary skill in the art:

> The contribution of the nervous system in inflammation has been recognized since Lewis (1932,

> 1936) proposed that the characteristic wheal and flare responses are mediated by the release of pro-inflammatory substances (described in detail below) from peripheral nerve endings of nociceptive afferent pathways.
>
> * * *
>
> The responses mediated by the peptides and transmitters released from sensory nerves include vasodilation (via cGRP release), and increased vascular permeability (via SP release) (Jancso et al., 1967; Lembeck and Holzer, 1979; Saria, 1984; McDonald et al., 1996; Anichini et al., 1997; Strittmatter et al., 1997; Carlson et al., 1996; Lundeberg et al., 1996). In addition, the activation of the immune system intiates the attraction of white cells, activation of phagocytic function of neutrophils and macrophages, stimulation of the increased production and release of inflammatory mediators from these cells and the degranulation of mast cells and local release of histamine (Helme and Andrews, 1979; Siato et al., 1986; Payan et al., 1984; Bar-Shavitz et al., 1980; Hartung et al., 1986; Johnson and Erdos, 1973; Naukkarinen et al., 1996). * * * The result of this neuroendocrine cascade of events has been termed, neurogenic inflammation (Jancso, 1967) and works as a central network modulating the events between the immune, nervous and endocrine systems.

('768 patent, Col. 2, lines 19-57).

Dr. Acquadro specifically compares the language used in the '768 patent to the present application's specification in paragraph 11 of his declaration. In characterizing the treatment of neurogenic inflammation with botulinum toxins, the '768 patent discloses that "cells that release neuropeptides and other mediators, activators or promoters of inflammation such as sensory and autonomic neurons and other secretory cells play a role in inflammation" and that "botulinum toxins block the actions of these mediators"

('768 patent, Col. 1, lines 24-29). Likewise, the instant application discloses that "this new bioeffect of anti-inflammatory action is explained by the resultant blockage of mast and nerve cell release of histamine and other preformed mediators which result in vascular dialation *[sic]*, increased permeability, altered sensory experience, edema and erythema", and that "it is thus a finding of this invention that inflammation is inhibited by administration of the subject chemodenervative agent" (Fourth paragraph of "Summary of Invention").

It is the Examiner's position that the applicant's argument that the cited references teaching neurogenic inflammation should be considered to be encompassed by the instant applicant is not persuasive. The Applicant respectfully requests that the Examiner reconsider this argument. Dr. Acquadro points out in paragraphs 12, 13 and 14 of his declaration that one of ordinary skill in the art, as of the earliest priority date of the pending application, August 25, 1998, would understand the disclosures of the instant specification to encompass and refer to the specific teachings of these references.

Consistent with the characterization of neurogenic inflammation of the '768 patent and of the instant application, Sann et al. (1996; enclosed herewith) discloses that "neurogenic inflammation appears to be mediated by a local release of sensory neuropeptides such as substance P (SP) and calcitonin gene-related peptide (CGRP)", and that "[sensory] nerves are capable of releasing neuropeptides such as SP, neurokinin A [NKA] and CGRP from their

peripheral endings which, in turn, provoke neurogenic inflammatory responses". (Acquadro Decl., ¶13).

As pointed out by Dr. Acquadro in paragraph 13 of his declaration, McDonald et al. (1996, enclosed herewith) also describes how one of ordinary skill in the art would understand the term "neurogenic inflammation" as of the earliest priority date of the pending application, August 25, 1998:

> The term neurogenic inflammation describes the increase in vascular permeability produced by substances released from sensory nerves.
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> * * *
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> Neurogenic inflammation is mediated by substance P and perhaps other peptides released from unmyelinated sensory axons.
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> * * *
>
> Substance P...appears to be the main active mediator, akthough other tachykinins, calcitonin gene-related peptide, and perhaps other peptides may also participate.
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> * * *
>
> [P]lasma leakage produced by histamine and bradykinin is partly dependent on sensory nerves.
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> * * *
>
> Neurogenic inflammation...has been identified in the dura, conjunctiva, eye lid, middle ear, oral mucosa, dental pulp, salivary gland ducts, esophagus, biliary system, anal mucosa, ureter, urinary bladder, skin, joints, nose, larynx, trachea, and bronchi[.]
>
> * * *
>
> [E]ach organ exhibits its own unique collection of effects of mediators released from sensory nerves.

The instant application discloses that "this new bioeffect of anti-inflammatory action is explained by the resultant blockage of mast and nerve cell release of histamine and other preformed mediators which result in vascular dilation, increased permeability, altered sensory experience, edema and erythema" (Fourth paragraph of "Summary of Invention"). In the third paragraph of "Mast Cells", the applicant cites a paper entitled "Histamine and Tumor Necrosis Factor-alpha Production From Purified Rat Brain Mast Cells Mediated by Substance P", thus disclosing the role played by substance P in triggering neurogenic inflammation, as described in the references cited above. It should thus be clear that the disclosure of the instant application would be understood by one of ordinary skill in the art to indicate that the applicant had in his possession, as of the earliest priority date of the pending application, August 25, 1998, the invention as particularly claimed in claims 17-23, because the application has a clear written description of the applicant's invention that chemodenervative pharmaceuticals such as botulinum toxins may be used to successfully treat neurogenic inflammation. (Acquadro Decl., ¶14).

Regarding claim 19, the Examiner failed to find support in the specification for "substance-P or many of the other specific mediators of Claim 19." However, Dr. Acquadro directs the Examiner's attention to the first paragraph of the "Background of the Invention" section of the specification where applicant explicitly refers to inflammation as involving "complement, arachidonic acid metabolites such as prostaglandin and leukotrienes,

cytokines, preformed mediators such as serotonin and histamine, and enzymes." (Acquadro Decl., ¶16). He states that one of ordinary skill in the art would understand that the term cytokine is defined in the art as referring to interleukin-1, interleukin-2, and tumor necrosis factor, and that 5-hydroxytryptamine is a synonym for serotonin as of the earliest priority date of the pending application, August 25, 1998. (Acquadro Decl., ¶16). In the first paragraph of the "Summary of the Invention", applicant explicitly states that "low dosages of the subject chemodenervative agent reduces histamine release and releases of other preformed mediators associated with mast cell degranulation." In the second and third paragraphs of the "Mast Cells" section of the specification, applicant explicitly refers to "preformed mediators such as histamine, newly formed mediators such as leukotrienes and prostaglandins, cytokines, including interleukin-5, interleukin-8, kininogenase, and platelet activating factor", as well as "tumor necrosis factor alpha" and "substance P". Thus, support for the terms "substance P", "interleukins", "tumor necrosis factor", and "serotonin" are explicitly found in the specification. (Acquadro Decl., ¶17). With regard to the other terms recited in claim 19, Dr. Acquadro explains that one of ordinary skill in the relevant art would clearly understand that applicant's explicit references in the specification to "preformed mediators", "cytokines", and "newly-formed mediators" encompasses all of the specific neurogenic inflammatory mediators enumerated in claim 19, and thus indicates that applicant was in possession of the invention in every particular

as claimed in claim 19 as of the earliest priority date of the pending application, August 25, 1998.

For claim 22, the Examiner failed to find support in the specification for a method of treating gout. In the second paragraph of the section of the specification entitled "Rheumatoid Arthritis", applicant refers to the invention as offering "a means of localized application of an anti-inflammatory agent which is injected directly into joints...which creates an effect on the rapid inflammatory response and peripheral neural elements governing the inflammatory response." In other words, it is within the scope of the invention as disclosed in the specification to treat neurogenic inflammation of the joints. Dr. Acquadro explains in paragraph 19 of his declaration that it is well understood by those of ordinary skill in the art that gout is a disease that is most fundamentally characterized by inflammatory response in the joints. Thus, one of ordinary skill in the relevant art would clearly conclude from applicant's statements in the specification regarding treatment of joint inflammation with chemodenervating pharmaceuticals that applicant was in possession of the invention as claimed in claim 22—including specifically the treatment of neurogenic inflammation caused by gout—as of the earliest priority date of the pending application, August 25, 1998. (Acquadro Decl., ¶19).

Regarding claim 23, the Examiner failed to find support in the specification for "treating the neurogenic inflammation by inhibiting histamine". However, as Dr. Acquadro points out in paragraphs 20 of his

declaration, Applicant discloses in numerous places in the specification that it is within the scope of the invention to reduce inflammation by inhibiting histamine. For example, in the first paragraph of the "Summary of the Invention", applicant explicitly states that "low dosages of the subject chemodenervative agent *reduces histamine releases*" (emphasis added). Claim 15 as originally filed recites "botulinum toxin immunotypes which block mast cell release of histamine". Furthermore, in the various examples disclosed later in the specification, such as successful treatment with chemodenervative pharmaceuticals of cholinergic urticaria, treatment of blepharoconjunctivitis, etc., it is well known in the relevant art that those disorders are always associated with increased histamine activity in the affected tissues, and that increased histamine activity is a major cause of the inflammation. It would thus be clear to one of skill in the relevant art that applicant, as of the earliest priority date of the pending application, August 25, 1998, was in possession of the invention as claimed in claim 23—including the treatment of neurogenic inflammation by inhibiting histamine.

C. Rejection of Claims 2-4 Under 35 U.S.C. § 112, ¶ 1 for Lack of Enablement

The Examiner rejected claims 2-4 on the ground that the specification disclosure is insufficient to enable one of ordinary skill in the art to practice the invention as broadly as claimed without undue experimentation.

The Examiner failed to find support in the specification for a method for reducing inflammation without causing substantial muscle weakness and with an effective dose of botulinum toxin of less than 2.5 units.

However, it is again respectfully submitted that the specification provides a number of working examples of treating inflammation with a chemodenervative pharmaceutical, such as botulinum toxin, without causing muscle weakness, and with doses within the claimed range. As previously argued and as stated by Dr. Acquadro in paragraph 15 of his declaration, the applicant discloses a working example wherein "botulinum toxin injected into red areas noted to be painful and thermally active in accordance with the subject invention has been demonstrated to block the erythema, pain, increased tenderness, and heat loss within the area", and that "minimum doses [for achieving this effect] range between 0.6 units to 15 units and are *far lower than that required to produce regional weakness"* (emphasis added) ("Spasmodic Torticollis", paragraph 4). As explained throughout the specification, and as well-understood by physicians for centuries, redness (erythema), pain, increased tenderness, and heat loss are some of the cardinal defining characteristics of inflammation. Furthermore, Dr. Acquadro points to another example where the applicant discloses as a working example "inject[ion] with .675 mouse units of botulinum toxin". ("Conjunctivitis", paragraph 3). According, the applicant requests that the Examiner reconsider these arguments supporting that one of ordinary skill in the art finds ample support in the specification for successfully treating inflammation with a chemodenervating agent, such as botulinum toxin, with a dose less than 2.5 units and without causing muscle weakness as of the earliest priority date of the pending application, August 25, 1998.

D. Rejection of Claims 1, 5-6, and 17-23 under 35 U.S.C. § 102(e) as Anticipated by U.S. Patent No. 6,063,768

The Examiner has rejected claims 1, 5-6, and 17-23 as being anticipated by U.S. Patent No. 6,063,768. (Sec. 13.) Applicant notes that he filed a Request to Declare Interference with the '768 patent on May 14, 2001. Once these claims are determined to be otherwise allowable, the Examiner may determine if an interference should be declared with respect to these claims in accordance with the applicable rules and standards.

E. Rejection of Claims 1, 5-8, 10-12, and 17-23 under 35 U.S.C. § 103(a) over U.S. Patent No. 6,063,768 in View of the Merck Manual

The Examiner rejected claims 1, 5-8, 10-12, and 17-23 as *prima facie* obvious over the '768 patent and the Merck Manual. Applicant notes that he filed a Request to Declare Interference with the '768 patent on May 14, 2001. Once these claims are determined to be otherwise allowable, the Examiner may determine if an interference should be declared with respect to these claims in accordance with the applicable rules and standards.

F. New Rejection of Claims 5-6 and 11-12 under 35 U.S.C. § 112, ¶2 for Indefiniteness

(a) Rejection of Claim 5 and 12 Under 35 U.S.C. § 112, ¶ 2 for Indefiniteness

The Examiner rejected claim 5 and 12 as indefinite, asserting that "includes" is vague and indefinite as it is impossible to establish the meters and bounds of the claims. The Examiner further requested that such term be amended to either "is" or "are". Applicant has amended claims 5 and 12 to remove the term "includes", and thus submits that claims 5 and 12 are now

allowable. Applicant has further amended claim 12 to change the term "rhinnitis" to "rhinitis". This amendment is made strictly to correct a typographical spelling error.

These amendments are made under the premise that the applicant is clarifying the claims and is not narrowing the scope of the claim in any matter. These amendments are made for the purpose of expediting prosecution and without prejudice to applicant's right to pursue the original claim in a continuation application.

(b) Rejection of Claim 6 Under 35 U.S.C. § 112, ¶ 2 for Indefiniteness

The Examiner rejected claim 6 as indefinite, asserting that "an other" is properly "another". Applicant has amended claim 6 to replace the term "an other" with "another", and thus submits that claim 6 is now allowable. This amendment is made under the premise that the applicant is clarifying the claim and is not narrowing the scope of the claim in any matter. This amendment is made for the purpose of expediting prosecution and without prejudice to applicant's right to pursue the original claim in a continuation application.

(c) Rejection of Claim 11 Under 35 U.S.C. § 112, ¶ 2 for Indefiniteness

The Examiner rejected claim 11 as indefinite, asserting that it fails to particularly point out and distinctly claim the subject matter which the applicant regards as the invention. However, the Examiner does not specifically point out the flaw within the claim. Presently, Claim 11 reads as

follows: "A method for treating classic type 1 hypersensitivity, comprising the step of administrating a chemodenvervating agent to the affected areas." Applicant respectfully argues that Claim 11 particularly points out and distinctly claims a method for treating classic type 1 hypersensitivity by utilizing the proper method claim terminology of "comprising the step of".

Additionally, Applicant has amended claim 11 to replace the phrase "the affected areas" with "an affected area", and thus submits that claim 11 is now allowable. This amendment is made under the premise that the applicant is clarifying the claim and is not narrowing the scope of the claim in any matter. This amendment is made for the purpose of expediting prosecution and without prejudice to applicant's right to pursue the original claim in a continuation application.

In light of the foregoing, as well as the content of the telephonic interview held with the Examiner on March 18, 2002, applicant submits that pending claims 2, 3, and 4 in this application are in condition for allowance, and a favorable action by the Examiner with respect to those claims is respectfully requested. Applicant further submits that claims 1, 5-8, 10-12, and 17-23 are in condition for allowance in every respect except with regard to the rejections over U.S. Patent No. 6,063,768. As explained above, applicant has filed a Request to Declare Interference between the present application and the '768 patent.

Applicant continues to be appreciative of the Examiner's prompt consideration of the claims and arguments presented. Applicant reiterates his respectful request that examination of the instant application continue to be with "special dispatch" under 37 C.F.R. § 1.607(a)(6).

If the Examiner is of the opinion that it would assist in placing claims 2, 3, and 4 in condition for allowance, and claims 1, 5-8, 10-12, and 17-23 in condition for allowance other than with regard to the prior art rejections over the '768 patent, or otherwise expedite prosecution, the applicant invites the Examiner to contact his counsel by telephone at the number listed below.

A one month extension of time is believed necessary for this filing and is hereby petitioned for. Additionally, enclosed herein is a supplemental Information Disclosure Statement pursuant to 37 C.F.R. §§ 1.56 and 1.97. It is believed that $253.00 are required for the IDS and extension of time. The Commissioner is hereby authorized to charge this fee, plus any additional fees which may be required, for these papers to Deposit Account Number 13-3250, Order No. 33677-00000.

Respectfully submitted,

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By: Claire A. Gil
Claire A. Gilmartin
Registration No. 51,735

MILBANK, TWEED, HADLEY & McCLOY LLP
1 Chase Manhattan Plaza
New York, NY 10005-1413
Telephone: (212) 530-5098
Facsimile: (212) 822-5098